

TENT COOPERATION TRE Y

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE
in its capacity as elected Office

Date of mailing (day/month/year) 07 March 2001 (07.03.01)	
International application No. PCT/US00/18347	Applicant's or agent's file reference A0000096-01E
International filing date (day/month/year) 05 July 2000 (05.07.00)	Priority date (day/month/year) 16 July 1999 (16.07.99)
Applicant DIXON, Alistair et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
18 January 2001 (18.01.01)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Juan Cruz Telephone No.: (41-22) 338.83.38
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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



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25 January 2001 (25.01.2001)

PCT

(10) International Publication Number
WO 01/05392 A3

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31/166, 31/136, 31/41, 31/495, 31/4453, 31/40, 31/44,
31/5375, 31/381, 31/341, 31/18, A61P 25/04

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(26) Publication Language: English

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60/144,292 16 July 1999 (16.07.1999) US

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(81) Designated States (*national*): AE, AG, AL, AU, BA, BB,
BG, BR, BZ, CA, CN, CR, CU, CZ, DM, DZ, EE, GD, GE,
HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV,
MA, MG, MK, MN, MX, MZ, NO, NZ, PL, RO, SG, SI,
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patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG,
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

(88) Date of publication of the international search report:
19 July 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHOD FOR TREATING CHRONIC PAIN USING MEK INHIBITORS

(57) Abstract: The invention features a method for treating chronic pain using a compound of formula (I) and 1 (A) which are shown in claim 1 and 26 of the application.

WO 01/05392 A3

INTERNATIONAL SEARCH REPORT

Intern. Application No

PCT/US 00/18347

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/196 A61K31/166 A61K31/136 A61K31/41 A61K31/495
A61K31/4453 A61K31/40 A61K31/44 A61K31/5375 A61K31/381
A61K31/341 A61K31/18 A61P25/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 00 35436 A (DUDLEY DAVID THOMAS ;FLORY CRAIG MASON (US); SALTIEL ALAN ROBERT () 22 June 2000 (2000-06-22) * Scheme 1, 2, 3, 4 * claims 1-5,10-13; examples ---	1,4,7,8, 26,29, 32,33, 38, 40-45, 49-51
P,Y	JI RU-RONG ET AL: "Nociceptive-specific activation of ERK in spinal neurons contributes to pain hypersensitivity." NATURE NEUROSCIENCE, vol. 2, no. 12, December 1999 (1999-12), pages 1114-1119, XP000978586 ISSN: 1097-6256 page 1117, column 2; figure 5 --- -/--	1-55

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

Date of the actual completion of the international search

12 January 2001

Date of mailing of the international search report

05/02/2001

Name and mailing address of the ISA

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Authorized officer

Veronese, A

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/18347

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 98 37881 A (BRIDGES ALEXANDER JAMES ;WARNER LAMBERT CO (US)) 3 September 1998 (1998-09-03) * See formula I, II, Scheme 1-3 * claims; examples ---	1-55
Y	WO 99 01421 A (DOHERTY ANNETTE MARIAN ;BARRETT STEPHEN DOUGLAS (US); BRIDGES ALEX) 14 January 1999 (1999-01-14) cited in the application claims; examples ---	1-55
X	T I SHUL'GA ET AL: "SYNTHESIS AND PHYSICOCHEMICAL AND BIOLOGICAL PROPERTIES OF DIPHENYLAMINE-2-CARBOXYLIC ACID DERIVATIVES" STN CHEMICAL ABSTRACTS,XX,XX, vol. 17, no. 109, 24 October 1988 (1988-10-24), XP002063639 abstract ---	26,29, 32,38
X	A N GAIDUKEVICH ET AL: "SYNTHESIS AND BIOLOGICAL ACTIVITY OF N-PHENYLANTHRANILIC ACID" STN CHEMICAL ABSTRACTS,XX,XX, vol. 11, no. 103, 16 September 1985 (1985-09-16), XP002063638 abstract ---	26,29, 32,41
X	KHALIFA M.: "Synthesis and biological activity of certain Derivatives of 2,4- dioxo- 1,2,3,4 tetrahydroquinazoline" PHARMAZIE, vol. 37, no. 2, 1982, pages 115-117, XP002157063 the whole document ---	26,29, 32,41
X	MOKHORT N A: "DEPENDENCE BETWEEN STRUCTURE, ANTIINFLAMMATORY, ANALGESIC, AND ANTIPYR" CHEMABS, AN = 1972:121461, 1972, XP002142610 abstract ---	26,29, 32,41
X	KHALIFA, M. ET AL: "Synthesis and biological activity of certain derivatives of 2,4-dioxo-1,2,3,4-tetrahydroquinazoline. Part 2" EGYPT. J. CHEM. (1983), VOLUME DATE 1982, 25(3), 285-91 , XP000978530 the whole document ---	26,29, 32,41

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/18347

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; GRYGLEWSKI, R. J.: "Structure-activity relations of some prostaglandin synthetase inhibitors" retrieved from STN Database accession no. 83:126083 XP002157064 abstract & PROSTAGLANDIN SYNTH. INHIBITORS - THEIR EFF. PHYSIOL. FUNCT. PATHOL. STATES, 'INT. SYMP.!' (1974), MEETING DATE 1973, 33-52. EDITOR(S): ROBINSON, HARRY J.; VANE, JOHN R. PUBLISHER: RAVEN, NEW YORK, N. Y. ,</p>	<p>26, 29, 32, 38</p>
A	<p>WO 99 01426 A (DOHERTY ANNETTE MARIAN ;BARRETT STEPHEN DOUGLAS (US); BRIDGES ALEX) 14 January 1999 (1999-01-14) claims; examples</p>	<p>1-25</p>
A	<p>DUESBERY N S ET AL: "MEK WARS, A NEW FRONT IN THE BATTLE AGAINST CANCER" NATURE MEDICINE, US, NATURE PUBLISHING, CO, vol. 5, no. 7, 1999, pages 736-737, XP000907246 ISSN: 1078-8956 the whole document</p>	<p>1-55</p>
A	<p>DUNCIA J V ET AL: "MEK inhibitors: the chemistry and biological activity of U0126, its analogs, and cyclization products" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, GB, OXFORD, vol. 8, no. 20, 20 October 1998 (1998-10-20), pages 2839-2844, XP004139571 ISSN: 0960-894X the whole document</p>	<p>1-55</p>

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/18347

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 0035436	A	22-06-2000	AU	2185800 A	03-07-2000
WO 9837881	A	03-09-1998	AU	5610398 A	18-09-1998
			ZA	9801578 A	02-09-1998
WO 9901421	A	14-01-1999	AU	8262698 A	25-01-1999
			BR	9810385 A	05-09-2000
			EP	0993437 A	19-04-2000
			HR	980369 A	30-04-1999
			ZA	9805726 A	27-01-1999
WO 9901426	A	14-01-1999	AU	8262798 A	25-01-1999
			BR	9810366 A	29-08-2000
			CN	1261877 T	02-08-2000
			EP	0993439 A	19-04-2000
			HR	980368 A	30-04-1999
			NO	996491 A	29-12-1999
			PL	337698 A	28-08-2000
			ZA	9805728 A	27-01-1999

REC'D 26 OCT 2001

WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference A0000096-01E	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US00/18347	International filing date (day/month/year) 05/07/2000	Priority date (day/month/year) 16/07/1999
International Patent Classification (IPC) or national classification and IPC A61K31/00		
Applicant WARNER-LAMBER COMPANY et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 9 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 18/01/2001	Date of completion of this report 24.10.2001
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Büttner, U Telephone No. +49 89 2399 7841 

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/18347

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, pages:

1-93 as originally filed

Claims, No.:

1-55 as originally filed

Drawings, sheets:

1/8-8/8 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US00/18347

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 1-55 (with respect to industrial applicability).

because:

- ☒ the said international application, or the said claims Nos. 1-55 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos. .
2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:
- ☐ the written form has not been furnished or does not comply with the standard.
- ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N) Yes: Claims 5-9, 30,31,34

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US00/18347

	No:	Claims	1-4, 10-29, 32, 33, 35-55
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-55
Industrial applicability (IA)	Yes:	Claims	
	No:	Claims	see section III

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 1-55 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following International Preliminary Examination has been carried out on the assumption that the present application is fully entitled to its priority date as claimed.

Reference is made to the following documents:

- D1: WO 99 01426 A
- D2: WO 99 01421 A
- D3: I. S. SHUL'GA ET AL: 'SYNTHESIS AND PHYSICOCHEMICAL AND BIOLOGICAL PROPERTIES OF DIPHENYLAMINE-2-CARBOXYLIC ACID DERIVATIVES' STN CHEMICAL ABSTRACTS,XX,XX, vol. 17, no. 109, 24 October 1988 (1988-10-24), XP002063639
- D4: A N GAIDUKEVICH ET AL: 'SYNTHESIS AND BIOLOGICAL ACTIVITY OF N-PHENYLANTHRANILIC ACID' STN CHEMICAL ABSTRACTS,XX,XX, vol. 11, no. 103, 16 September 1985 (1985-09-16), XP002063638
- D5: KHALIFA M.: 'Synthesis and biological activity of certain Derivatives of 2,4- dioxo- 1,2,3,4 tetrahydroquinazoline' PHARMAZIE, vol. 37, no. 2, 1982, pages 115-117, XP002157063
- D6: KHALIFA, M. ET AL: 'Synthesis and biological activity of certain derivatives of 2,4-dioxo-1,2,3,4-tetrahydroquinazoline. Part 2' EGYPT. J. CHEM. (1983), VOLUME DATE 1982, 25(3), 285-91 , XP000978530

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/18347

- D7: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; GRYGLEWSKI, R. J.: 'Structure-activity relations of some prostaglandin synthetase inhibitors' retrieved from STN Database accession no. 83:126083 XP002157064 & PROSTAGLANDIN SYNTH. INHIBITORS - THEIR EFF. PHYSIOL. FUNCT. PATHOL. STATES, [INT. SYMP.] (1974), MEETING DATE 1973, 33-52. EDITOR(S): ROBINSON, HARRY J.; VANE, JOHN R. PUBLISHER: RAVEN, NEW YORK, N. Y. ,
- D8: DUESBERY N S ET AL: 'MEK WARS, A NEW FRONT IN THE BATTLE AGAINST CANCER' NATURE MEDICINE, US, NATURE PUBLISHING, CO, vol. 5, no. 7, 1999, pages 736-737, XP000907246 ISSN: 1078-8956

Claims 1-25

claims 1-4 and 10-25

(N)(IS)

Claim 1 describes the use of phenylamino derivates following formula (I) of claim 1 for treating chronic pain.

D1 discloses phenylamino derivates following formula (I) for treatment of cancer (D1, P9 L5, claim 24) and diabetes (D1, P9 L7, claim 29).

Additionally D8 (whole document) discloses a phenylamino derivate following formula (I) of claim 1 for treatment of cancer.

According to the description of the present application cancer (P1, L32) and diabetes (P1, L15; claim 4) are associated with neuropathic pain. Thus the treatment of cancer and diabetes implies the treatment of the associated pain. Consequently the subject matter of claims 1-4 and 10-25 is not novel and inventive (Article 33(2) and (3) PCT).

claims 5-9

(N) D1 discloses the use of phenylamino derivates following formula (I) for treatment of proliferative diseases like cancer. Malfunctions as defined in claims 5-9 are not disclosed. Therefore the subject matter of claims 5-9 is considered to be novel.

(IS) There is no evidence in the description of the present application, which suggests that compounds as defined in claim 1 have an effect for the treatment of chronic

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/18347

pain associated with malfunctions described in claims 5-9. All biological examples (P46-53) are based on the treatment of diabetes. However no basis for the treatment of chronic pain associated with the claimed malfunctions is given. If the applicant is of the opinion that the treatment of the malfunctions defined in claims 5-9 is evident from the treatment of diabetes, he should consider that the same conclusion could be made from D1 (P9 L7, claim 29) which discloses already the treatment of diabetes with phenylamino derivatives following formula (I).

Therefore the subject matter of claims 5-9 is not inventive (Article 33(3) PCT).

Claims 26-55

claims 26-29, 32, 33, 35-55

(N)(IS)

Independent claim 26 describes the use of phenylamino derivatives following formula (I)(A) of claim 26 for treating chronic pain.

D2 discloses phenylamino derivatives following formula (I)(A) of claim 26 for treatment of cancer (D2, P7 L7, claim 26), diabetes (D2, P7 L7, claim 31) and inflammation (D2, Abstract).

Documents D3 (compound 116702-62-6P), D4 (compound 90656-46-5P) D5 (compound 4a (Scheme 2)), D6 (compound IV.2 Scheme 2), D7 (compound 13278-40-5) disclose compounds falling under formula (I)(A) of claim 26. These documents describe the use of these compounds as inflammation inhibitors or antiarthritics (D4).

According to the description of the present application cancer (P1, L32), diabetes (P1, L15; claim 29), inflammation (claims 29 and 32) and arthritis (P1 L19, claims 29 and 33) are associated with neuropathic pain. Thus the treatment of cancer, diabetes inflammation and arthritis implies the treatment of the associated pain. Consequently the subject matter of claim 26-29, 32, 33 35-55 is not novel and inventive (Article 33(2) and (3)).

claims 30, 31, 34

(N) D2 discloses the use of phenylamino derivatives following formula (I)(A) of claim 26 for treatment of proliferative diseases like cancer and inflammation. Malfunctions as defined in claims 30, 31, 34 are not disclosed. Therefore the subject matter of

claims 30, 31, 34 is considered to be novel.

- (IS)** There is no evidence in the description of the present application, which suggests that compounds as defined in claim 26 have an effect for the treatment of chronic pain associated with malfunctions described in claims 30, 31, 34. All biological examples (P46-53) are based on the treatment of diabetes. However no basis for the treatment of chronic pain associated with the claimed malfunctions is given. If the applicant is of the opinion that the treatment of chronic pain associated with malfunctions defined in claims 30, 31, 34 is evident from the treatment of diabetes, he should consider that the same conclusion could be made from D2 (D2, P7 L7, claim 31) which discloses already the treatment of diabetes with phenylamino derivatives following formula (I)(A) of claim 26.

Furthermore there is no evidence or data in the description of the present application, which suggest that chronic pain at all can be treated by compounds defined in claims 26-55. None of the compounds tested in the biological examples 1-3 (P46-53) contains a compound falling under formula (I)(A) of claim 26. Therefore the subject matter of claims 30, 31, 34 is not inventive (Article 33(3) PCT).

- (IA)** For the assessment of the present claims 1-55 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI

Certain documents cited

The following document is not considered to be part of the prior art (Rule 64.3 PCT).

D9: WO 00 42022 A

Priority Data: 16.12.198 and 10.11.1999

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/18347

Filing Date: 15.12.1999

Publication Date: 22.07.2000

D9 discloses the use of compounds following formula (I) of claim 1 and formula (I)(A) of claim 26 for the treatment of different types of arthritis (D9; P24, L19-26). According to the description of the present application (P1, L19) diseases associated with neuropathic pain include arthritis.

In case the present application would enter the European Phase the above-mentioned document, which is cited in the ISR, would be prejudicial to the novelty of the subject matter of claims 1-4 and 8, 10-25, 26-29 and 33, 35-55 of the present application.

Re Item VIII

Certain observations on the international application

Claim 26 is not clear (Article 6 PCT). The meaning of the "O" in the middle of the claim is not clear.

The compounds 3,4 Difluoro-2-(2-chloro-4-iodo-phenylamino)-N-cyclobutylmethoxy-benzamide and the following compounds of claim 17 do not fall into the formula of claim 13 from which they should be dependent.

The compound 5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-benzyl)-N-... (Claim 19, P99, L 23) does not fall under formula (I) of claim 1.

The compound on Page 100, Line 29 of claim 19 does not fall into the formula of claim 13 from which it should be dependent.

2 compounds described in claim 37 do not fall under formula (I)(A) of claim 26.

Compound PD297447 (P52) could not be identified.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference A0000096-01E	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US 00/ 18347	International filing date (day/month/year) 05/07/2000	(Earliest) Priority Date (day/month/year) 16/07/1999
Applicant WARNER-LAMBER COMPANY et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :



contained in the international application in written form.



filed together with the international application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.



the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,



the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,



the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.



as suggested by the applicant.



because the applicant failed to suggest a figure.



because this figure better characterizes the invention.



None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 00/18347

Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

The invention features a method for treating chronic pain using a compound of formula (I) and 1 (A) which are shown in claim 1 and 26 of the application.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/18347

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 A61K31/196 A61K31/166 A61K31/136 A61K31/41 A61K31/495 A61K31/4453 A61K31/40 A61K31/44 A61K31/5375 A61K31/381 A61K31/341 A61K31/18 A61P25/04		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 00 35436 A (DUDLEY DAVID THOMAS ;FLORY CRAIG MASON (US); SALTIEL ALAN ROBERT () 22 June 2000 (2000-06-22) * Scheme 1, 2, 3, 4 * claims 1-5,10-13; examples ---	1, 4, 7, 8, 26, 29, 32, 33, 38, 40-45, 49-51
P, Y	JI RU-RONG ET AL: "Nociceptive-specific activation of ERK in spinal neurons contributes to pain hypersensitivity." NATURE NEUROSCIENCE, vol. 2, no. 12, December 1999 (1999-12), pages 1114-1119, XP000978586 ISSN: 1097-6256 page 1117, column 2; figure 5 --- <div style="text-align: center;">-/--</div>	1-55
<div style="display: flex; justify-content: space-between;"> <input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex. </div>		
° Special categories of cited documents :		
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>*A* document defining the general state of the art which is not considered to be of particular relevance</p> <p>*E* earlier document but published on or after the international filing date</p> <p>*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>*O* document referring to an oral disclosure, use, exhibition or other means</p> <p>*P* document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>*&* document member of the same patent family</p> </div> </div>		
Date of the actual completion of the international search	Date of mailing of the international search report	
12 January 2001	05/02/2001	
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Veronese, A	

INTERNATIONAL SEARCH REPORT

International Application No

/US 00/18347

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 98 37881 A (BRIDGES ALEXANDER JAMES ;WARNER LAMBERT CO (US)) 3 September 1998 (1998-09-03) * See formula I, II, Scheme 1-3 * claims; examples ---	1-55
Y	WO 99 01421 A (DOHERTY ANNETTE MARIAN ;BARRETT STEPHEN DOUGLAS (US); BRIDGES ALEX) 14 January 1999 (1999-01-14) cited in the application claims; examples ---	1-55
X	T I SHUL'GA ET AL: "SYNTHESIS AND PHYSICO-CHEMICAL AND BIOLOGICAL PROPERTIES OF DIPHENYLAMINE-2-CARBOXYLIC ACID DERIVATIVES" STN CHEMICAL ABSTRACTS,XX,XX, vol. 17, no. 109, 24 October 1988 (1988-10-24), XP002063639 abstract ---	26,29, 32,38
X	A N GAIDUKEVICH ET AL: "SYNTHESIS AND BIOLOGICAL ACTIVITY OF N-PHENYLANTHRANILIC ACID" STN CHEMICAL ABSTRACTS,XX,XX, vol. 11, no. 103, 16 September 1985 (1985-09-16), XP002063638 abstract ---	26,29, 32,41
X	KHALIFA M.: "Synthesis and biological activity of certain Derivatives of 2,4- dioxo- 1,2,3,4 tetrahydroquinazoline" PHARMAZIE, vol. 37, no. 2, 1982, pages 115-117, XP002157063 the whole document ---	26,29, 32,41
X	MOKHORT N A: "DEPENDENCE BETWEEN STRUCTURE, ANTIINFLAMMATORY, ANALGESIC, AND ANTIPYR" CHEMABS, AN = 1972:121461, 1972, XP002142610 abstract ---	26,29, 32,41
X	KHALIFA, M. ET AL: "Synthesis and biological activity of certain derivatives of 2,4-dioxo-1,2,3,4-tetrahydroquinazoline. Part 2" EGYPT. J. CHEM. (1983), VOLUME DATE 1982, 25(3), 285-91 , XP000978530 the whole document ---	26,29, 32,41

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/18347

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; GRYGLEWSKI, R. J.: "Structure-activity relations of some prostaglandin synthetase inhibitors" retrieved from STN Database accession no. 83:126083 XP002157064 abstract & PROSTAGLANDIN SYNTH. INHIBITORS - THEIR EFF. PHYSIOL. FUNCT. PATHOL. STATES, 'INT. SYMP.! (1974), MEETING DATE 1973, 33-52. EDITOR(S): ROBINSON, HARRY J.; VANE, JOHN R. PUBLISHER: RAVEN, NEW YORK, N. Y. ,</p>	26, 29, 32, 38
A	<p>--- WO 99 01426 A (DOHERTY ANNETTE MARIAN ; BARRETT STEPHEN DOUGLAS (US); BRIDGES ALEX) 14 January 1999 (1999-01-14) claims; examples</p>	1-25
A	<p>--- DUESBERY N S ET AL: "MEK WARS, A NEW FRONT IN THE BATTLE AGAINST CANCER" NATURE MEDICINE, US, NATURE PUBLISHING, CO, vol. 5, no. 7, 1999, pages 736-737, XP000907246 ISSN: 1078-8956 the whole document</p>	1-55
A	<p>--- DUNCIA J V ET AL: "MEK inhibitors: the chemistry and biological activity of U0126, its analogs, and cyclization products" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, GB, OXFORD, vol. 8, no. 20, 20 October 1998 (1998-10-20), pages 2839-2844, XP004139571 ISSN: 0960-894X the whole document</p> <p>-----</p>	1-55

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/18347

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 0035436	A	22-06-2000	AU	2185800 A	03-07-2000
WO 9837881	A	03-09-1998	AU	5610398 A	18-09-1998
			ZA	9801578 A	02-09-1998
WO 9901421	A	14-01-1999	AU	8262698 A	25-01-1999
			BR	9810385 A	05-09-2000
			EP	0993437 A	19-04-2000
			HR	980369 A	30-04-1999
			ZA	9805726 A	27-01-1999
WO 9901426	A	14-01-1999	AU	8262798 A	25-01-1999
			BR	9810366 A	29-08-2000
			CN	1261877 T	02-08-2000
			EP	0993439 A	19-04-2000
			HR	980368 A	30-04-1999
			NO	996491 A	29-12-1999
			PL	337698 A	28-08-2000
			ZA	9805728 A	27-01-1999